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EXAMINER
KIM, TAEYOON

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
06/14/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/584,028	TAKAKURA ET AL.	
	Examiner	Art Unit	
	Taeyoon Kim	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-16 and 18-26* is/are pending in the application.

4a) Of the above claim(s) *20-22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16,18,19,23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 3/24/2010 has been received and entered into the case.

Claims 1-11, 17 and 27 are canceled, claims 20-22 and 24 have been withdrawn from consideration as being drawn to non-elected subject matter, and claims 12-16, 18, 19, 23, 25 and 26 have been considered on the merits. All arguments have been fully considered.

The claim rejection under 35 U.S.C.§103 has been withdrawn. Applicant's arguments with respect to claims 12-19, 23 and 25-27 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-16, 18, 19, 23, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims disclose the method of differentiating mammalian bone marrow cells or cord blood-derived cells into myocardial precursor cells or myocardial cells by culturing the cells with fat cells isolated from mammalian fat tissues or a culture supernatant.

The current amendment introduces a new limitation of "fat cells isolated from mammalian fat tissues", which is narrower limitation than the original disclosure of "cells isolated from mammalian fat tissues". According to the specification, the cells isolated from fat tissues include fat cells, fat precursor cells, and somatic stem cells (p.6, lines 11-12). Therefore, the term "fat cells" in this context is considered as adipocytes.

The specification, however, discloses no adequate support that only "fat cells" used in the method of claimed invention. Rather the specification discloses the cells derived from fat tissues, which includes fat cells, fat precursor cells and somatic stem cells, are used in the claimed method.

Therefore, the new limitation of using "fat cells" in the current amendment introduces a new matter to the application.

Applicant alleged that the specification discloses the isolation and culture of fat cells from fat tissue citing Example 1 at p.12, line 11, which specifies "culturing mouse fat cells." This argument is not persuasive. It is acknowledged that the specification discloses the alleged description (see below).

> Example 1 : Differentiation of fat tissues into myocardial cells
>
> Fat tissues (about 1.5 ml) were removed from the cervical or abdominal region of a mouse or rat, the tissues were sliced using ophthalmic surgery scissors, and the sliced tissues were immersed in 1 ml of dispase solution at 37°C for 15 minutes to loosen the cells. The cells were then filtered through a 40-micron nylon mesh filter, sowed at a cell density of 1 x10^6 cells/ml, and then subjected to two-dimensional culture on a 24-well culture dish (diameter: about 1.3 cm) in 5% *C02* at 37OC using a DMEM medium containing 10% FCS.
>
> Fig. 1 shows the results of culturing mouse fat cells. Beating myocardial cell-like cells were observed 3 days after the initiation of culture, and proliferation of spherical myocardial precursor/stem cell-like cells was initiated simultaneously therewith. Myocardial cells can be identified by abundant mitochondria, ANP granules, and Z bands with the use of a stereoscopic microscope, and by morphological traits such as beating and spindle shapes with the use of an inverted microscope. Spindle-shaped cells appeared approximately 1 week after the initiation of culture, and a sheet structure was observed 2 or 3 weeks after

> the initiation of culture. Colonies (approximately 200 to 300) of myocardial cells were observed in each well 1 week after the initiation of culture.

Applicant indicates that the last paragraph of the above cited paragraphs of the specification discloses "culturing mouse fat cells", and this disclosure provides adequate support for the use of only “fat cells” in the claimed methods. This particular sentence does not provide any description whether the "fat cells" are isolated, or the “fat cells” are intended to be adipocyte per se, or "fat tissue-derived cells”. In fact, on p.4 of the specification, there is a brief description on figure 1.

> Fig. 1 shows the results of culturing fat tissues (differentiation into myocardial cells)
> (A: at the time of initiation of culture; B. 7 days after the initiation of culture; C: 14 days after the initiation of culture; D. 28 days after the initiation of culture).

As shown above, Fig. 1 is directed to culturing "fat tissues" and there is no indication that "fat cells" (or adipocyte) are isolated and cultured alone with bone marrow or cord blood-derived cells as claimed.

The question in this particular rejection is whether the specification discloses to use isolated “fat cells”, which is interpreted as “adipocyte” rather than any other cells present in fat tissue. Throughout the specification, the method of the invention is directed to use cells derived from fat tissue, and the cells include fat cells (i.e. adipocyte), fat precursor cells, and somatic stem cells. There is no disclosure that only "fat cells" or "adipocyte" isolated from the fat tissue being used in the method. Therefore, the phrase "fat cells isolated from mammalian fat tissues", which is interpreted as "adipocyte isolated from mammalian fat tissues", does not have an adequate support from the specification.

It is recommended to amend this particular phrase to include specific cell types or marker expression as disclosed in p.6, lines 11-14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-16, 18, 19, 23, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umezawa et al. (US 2002/0142457; of record) in view of Naughton et al. (US 4,963,489; of record) in further view of Egger et al. (2004, Nature; of record), Bonnet (2003, Clin. Exp. Med.; of record), Gilmore et al. (2000, Exp. Hematol.; of record) and Lee et al. (2004, Blood; of record).

Umezawa et al. teach a method of differentiating multipotential stem cells from bone marrow or umbilical cord blood derived cells into cardiomyocyte in vitro (par. 11, 12, 17-19).

Umezawa et al. teach that the cells having the potential to differentiate into

cardiomyocytes are cultured for 24 hours in the presence of 5-azacytidine, and then further cultured for 2-3 weeks to obtain cardiomyocytes (par. 134), satisfying the limitation of claim 13.

Umezawa et al. teach the expression of a-skeletal actin and a-cardiac actin (sarcomeric actin) in the cardiomyocytes differentiated from bone marrow (par. 330), and thus meet the limitation of claim 19.

Umezawa et al. do not teach co-culture of fat cells (adipocytes) isolated from fat tissues with bone marrow cells or cord blood derived cells.

Naughton et al. teach a method of co-culturing bone marrow cells and stromal cells including adipocytes (fat cells) as a stromal support matrix (see abstract; col. 2, lines 55-66).

It would therefore have been obvious for the person of ordinary skill in the art at the time the invention was made to use stromal cells including adipocytes of Naughton et al. in the method of Umezawa et al.

The skilled artisan would have been motivated to make such a modification because Naughton et al. teach the stromal support matrix would sustain active proliferation of the culture for a long period of time, and various cell types including bone marrow cells can be grown in the stromal support matrix (col.3, lines 5-36), and Umezawa et al.'s method is also directed to the proliferation/expansion of cells capable of differentiating into cardiomyocytes (abstract).

The person of ordinary skill in the art would have had a reasonable expectation of success in using stromal support matrix including adipocytes taught by Naughton et al. in the method of Umezawa et al.

Since the method of Umezawa et al. utilizes 5-azacytidine, this is considered to satisfy the step of inducing bone marrow cells or cord blood-derived cells to myocardial cells.

With regard to the limitation of "without genetic engineering", the treatment with 5-azacytidine to the mesenchymal stem cells is not considered as a genetic engineering. Rather it is considered as epigenetic modification since 5-azacytidine is a DNA methylation inhibitor according to Egger et al. (Abstract and Table 2).

With regard to the limitation of using cytokines in the method of claims 14, 15 and 23, Umezawa et al. teach the use of growth factors or cytokines such as PDGF, FGF-8 (EGF family member), ET-1 or BMP-4 for differentiation of the mesenchymal stem cells into cardiomyocytes (par. 46-48).

With regard to the limitation to the bone marrow cells being MSCs or HSCs in claim 16, it is well known in the art that bone marrow cells comprise both HSCs and MSCs according to Bonnet (entire document), and thus the multipotential stem cells of bone marrow of Umezawa et al. inherently comprise HSCs as well as MSCs.

With regard to the limitation of ratio between bone marrow cells and fat tissue derived cells being 1:1 to 1:10 in claim 18 or 1:4 as in claim 26, it would have been obvious to a person of ordinary skill in the art to optimize the ratio between bone marrow cells and fat tissue derived cells for the method of Umezawa et al. in view of Rangappa et al. This is because a person of ordinary skill in the art would recognize that the mixing ratio between two groups of cell population in co-culture system would be considered as a result effective variable for the method. The variables would be routinely optimized by one of ordinary skill in the art in practicing the invention disclosed by those references. Generally, differences in concentration, and thus the ratio of the contents, will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made especially in the absence of evidence to the contrary.

With regard to the limitation to the cord blood-derived cells being mononuclear cells, Umezawa et al. is silent which cells the multipotential stem cells (mesenchymal stem cells) of umbilical cord blood is derived from. However, it is well known in the art that multipotential stem cells, including HSCs and MSCs according to Bonnet, can be derived from umbilical cord blood-derived mononuclear cells according to Gilmore et al. (p.1298, Materials and Method) and Lee et al. (see p.1670, MSC isolation and culture). Thus, the multipotential stem cells of Umezawa et al. would be inherently derived from mononuclear cells of umbilical cord blood.

With regard to the limitation drawn to the bone marrow cells or cord blood-derived cells being derived from the same species as the fat tissues, it is submitted that since it is extremely well known in the art that the cells derived from the method of Umezawa et al. can be used for

transplantation for repairing or reconstructing myocardium (par. 3 of Umezawa et al.), it would have been obvious to a person of ordinary skill in the art to combine the cells from the same species (allogeneic) or even autologous sources for the use of the cells in myocardial repair.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taeyoon Kim whose telephone number is (571)272-9041. The examiner can normally be reached on 8:00 am - 5:00 pm ET (Mon-Thu).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Taeyoon Kim/
Primary Examiner, Art Unit 1651